# Appendix Table 6. EtD for vasopressin in shock recommendation

|  |  |
| --- | --- |
| Question | |
| **Should vasopressin and norepinephrine vs. norepinephrine alone be used for patients who remain hypotensive despite fluid resuscitation?** | |
| **Population:** | Patients with ALF or ACLF who remain hypotensive despite fluid resuscitation |
| **Intervention:** | vasopressin and norepinephrine |
| **Comparison:** | norepinephrine alone |
| **Main outcomes:** | Mortality; Mortality - cirrhosis studies only; Digital ischemia; Digital ischemia - cirrhosis studies only; |
| **Setting:** | acute and chronic liver failure |

Assessment

|  |  |  |
| --- | --- | --- |
| Problem Is the problem a priority? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Desirable Effects How substantial are the desirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with norepinephrine alone** | **Risk difference with vasopressin and norepinephrine** | | Mortality follow up: 28 days | 2904 (17 RCTs) | ⨁⨁◯◯ LOWa,b | **RR 0.89** (0.82 to 0.97) | Study population | | | 407 per 1,000 | **45 fewer per 1,000** (73 fewer to 12 fewer) |  1. Results lose statistical significance and point estimate moves towards no effect when analyses limited to studies at low risk of bias. 2. Studies in distributive shock rather than patients with acute and chronic liver failure.  | **Outcomes** | **With norepinephrine alone** | **With vasopressin and norepinephrine** | **Difference** | **Relative effect (95% CI)** | | --- | --- | --- | --- | --- | | Mortality follow up: 28 days | 407 per 1,000 | **363 per 1,000** (334 to 395) | **45 fewer per 1,000** (73 fewer to 12 fewer) | **RR 0.89** (0.82 to 0.97) | | Mortality - cirrhosis studies only follow up: median 28 days | 694 per 1,000 | **527 per 1,000** (430 to 652) | **167 fewer per 1,000** (264 fewer to 42 fewer) | **RR 0.76** (0.62 to 0.94) | | Digital ischemia | 17 per 1,000 | **42 per 1,000** (24 to 72) | **24 more per 1,000** (6 more to 55 more) | **RR 2.38** (1.37 to 4.12) | | Digital ischemia - cirrhosis studies only | 95 per 1,000 | **286 per 1,000** (100 to 814) | **190 more per 1,000** (5 more to 719 more) | **RR 3.00** (1.05 to 8.55) | | Proposal for small - all agree |
| Undesirable Effects How substantial are the undesirable anticipated effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with norepinephrine alone** | **Risk difference with vasopressin and norepinephrine** | | Mortality follow up: 28 days | 2904 (17 RCTs) | ⨁⨁◯◯ LOWa,b | **RR 0.89** (0.82 to 0.97) | Study population | | | 407 per 1,000 | **45 fewer per 1,000** (73 fewer to 12 fewer) |  1. Results lose statistical significance and point estimate moves towards no effect when analyses limited to studies at low risk of bias. 2. Studies in distributive shock rather than patients with acute and chronic liver failure.  | **Outcomes** | **With norepinephrine alone** | **With vasopressin and norepinephrine** | **Difference** | **Relative effect (95% CI)** | | --- | --- | --- | --- | --- | | Mortality follow up: 28 days | 407 per 1,000 | **363 per 1,000** (334 to 395) | **45 fewer per 1,000** (73 fewer to 12 fewer) | **RR 0.89** (0.82 to 0.97) | | Mortality - cirrhosis studies only follow up: median 28 days | 694 per 1,000 | **527 per 1,000** (430 to 652) | **167 fewer per 1,000** (264 fewer to 42 fewer) | **RR 0.76** (0.62 to 0.94) | | Digital ischemia | 17 per 1,000 | **42 per 1,000** (24 to 72) | **24 more per 1,000** (6 more to 55 more) | **RR 2.38** (1.37 to 4.12) | | Digital ischemia - cirrhosis studies only | 95 per 1,000 | **286 per 1,000** (100 to 814) | **190 more per 1,000** (5 more to 719 more) | **RR 3.00** (1.05 to 8.55) | |  |
| Certainty of evidence What is the overall certainty of the evidence of effects? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ● Low ○ Moderate ○ High ○ No included studies | | **Outcomes** | **№ of participants (studies) Follow up** | **Certainty of the evidence (GRADE)** | **Relative effect (95% CI)** | **Anticipated absolute effects\* (95% CI)** | | | --- | --- | --- | --- | --- | --- | | **Risk with norepinephrine alone** | **Risk difference with vasopressin and norepinephrine** | | Mortality follow up: 28 days | 2904 (17 RCTs) | ⨁⨁◯◯ LOWa,b | **RR 0.89** (0.82 to 0.97) | Study population | | | 407 per 1,000 | **45 fewer per 1,000** (73 fewer to 12 fewer) |  1. Results lose statistical significance and point estimate moves towards no effect when analyses limited to studies at low risk of bias. 2. Studies in distributive shock rather than patients with acute and chronic liver failure. |  |
| Values Is there important uncertainty about or variability in how much people value the main outcomes? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability |  | some uncertainty in the balance of digital ischemia/mortality for patients |
| Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know |  |  |
| Resources required How large are the resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know |  |  |
| Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Very low ○ Low ○ Moderate ○ High ● No included studies |  |  |
| Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies |  |  |
| Equity What would be the impact on health equity? | | |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know |  |  |
| Acceptability Is the intervention acceptable to key stakeholders? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |
| Feasibility Is the intervention feasible to implement? | | |
| Judgement | Research evidence | Additional considerations |
| ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know |  |  |

Summary of judgements

|  | **Judgement** | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | Trivial | **Small** | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | **Small** | Trivial |  | Varies | Don't know |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | **Does not favor either the intervention or the comparison** | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Feasibility** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |

Type of recommendation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | Conditional recommendation against the intervention | **Conditional recommendation for either the intervention or the comparison** | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○ | ○ | **●** | ○ | ○ |

| Vasopressin and norepinephrine compared to norepinephrine alone for patients who remain hypotensive despite fluid resuscitation  **Bibliography: McIntyre WF, Um KJ, Alhazzani W et al. Association of vasopressin plus catecholamine vasopressors vs catecholamines alone with atrial fibrillation in patients with distributive shock: A systematic review and meta-analysis. JAMA 2018; 319(18): 1889-1990.** | | | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Quality assessment** | | | | | | | **Summary of findings** | | | | |
| **№ of participants (studies) Follow-up** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Overall quality of evidence** | **Study event rates (%)** | | **Relative effect (95% CI)** | **Anticipated absolute effects** | |
| **With norepinephrine alone** | **With vasopressin and norepinephrine** | **Risk with norepinephrine alone** | **Risk difference with vasopressin and norepinephrine** |
| **Mortality (follow up: 28 days)** | | | | | | | | | | | |
| 2904 (17 RCTs) | serious a | not serious | serious b | not serious | none | ⨁⨁◯◯ LOW | 591/1451 (40.7%) | 532/1453 (36.6%) | **RR 0.89** (0.82 to 0.97) | 407 per 1,000 | **45 fewer per 1,000** (from 73 fewer to 12 fewer) |
| **Mortality - cirrhosis studies only (follow up: median 28 days)** | | | | | | | | | | | |
| 292 (3 RCTs) | very serious c | not serious | not serious | not serious | none | ⨁⨁◯◯ LOW | 102/147 (69.4%) | 74/145 (51.0%) | **RR 0.76** (0.62 to 0.94) | 694 per 1,000 | **167 fewer per 1,000** (from 264 fewer to 42 fewer) |
| **Digital ischemia** | | | | | | | | | | | |
| 1963 (9 RCTs) | not serious | not serious | very serious d | not serious | none | ⨁⨁◯◯ LOW | 17/973 (1.7%) | 41/990 (4.1%) | **RR 2.38** (1.37 to 4.12) | 17 per 1,000 | **24 more per 1,000** (from 6 more to 55 more) |
| **Digital ischemia - cirrhosis studies only** | | | | | | | | | | | |
| 84 (1 RCT) | serious c | not serious | serious d | not serious | none | ⨁⨁◯◯ LOW | 4/42 (9.5%) | 12/42 (28.6%) | **RR 3.00** (1.05 to 8.55) | 95 per 1,000 | **190 more per 1,000** (from 5 more to 719 more) |

**CI:** Confidence interval; **RR:** Risk ratio

#### Explanations

a. Results lose statistical significance and point estimate moves towards no effect when analyses limited to studies at low risk of bias.

b. Studies in distributive shock rather than patients with acute and chronic liver failure.

c. All trials were at high ROB

d. Definitions for digital ischemia varies across studies.